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# Endothelial Adhesion Molecules and Multiple Organ Failure in Patients With Severe Sepsis

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## ABSTRACT

### Objective

To determine if serum levels of endothelial adhesion molecules are associated with development of multiple organ failure (MOF) and in-hospital mortality in adult patients with severe sepsis.

### Design

This study was a secondary data analysis of a prospective cohort study.

### Setting

Patients were admitted to two tertiary intensive care units in San Antonio, TX, between 2007 and 2012.

### Patients

Patients with severe sepsis at the moment of ICU admission were enrolled. Inclusion criteria were consistent with previously published criteria for severe sepsis or septic shock in adults. Exclusion criteria included immunosuppressive medications or conditions.

### Interventions

None.

### Measurements

Baseline endothelial adhesion molecules serum levels of Intracellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1) and Vascular Endothelial Growth Factor (VEGF) were obtained within 24-48 hours of development of organ dysfunction. The primary outcome was development of MOF ($\geq$2 organ dysfunction) and

the secondary outcome was in-hospital mortality.

**Main results**

Forty-eight patients were enrolled in this study, of which 29 (60%) developed MOF. Severe septic patients that developed MOF had higher levels of VCAM-1 ($p<0.01$) and ICAM-1 ($p<0.02$), but not VEGF levels ($p=0.7$). The area under the curve (AUC) to predict MOF according to VCAM-1, ICAM-1 and VEGF was 0.71, 0.73, and 0.54, respectively. Only VCAM-1 was associated with in-hospital mortality ($p<0.04$). These associations were maintained even after controlling for APACHE scores using logistic regression.

**Conclusions**

High levels of VCAM-1 and ICAM-1 were associated with the development of MOF. VCAM-1 levels are associated with in-hospital mortality. Further studies should evaluate the diagnostic and prognostic role of these biomarkers in septic patients.

## INTRODUCTION

Mortality rates for patients with severe sepsis and septic shock range from 40-60%, costing the U.S. health care system $17 billion annually[1]. Research is needed to identify patients with severe sepsis to expedite initiation of effective treatments. Hemodynamic parameters and lactate levels are useful in predicting multiple organ failure (MOF) in patients with sepsis, but only change when organ perfusion is already compromised[2,3]. Early clinical deterioration and death is related with a complex interaction between inflammation and coagulation that leads to organ dysfunction[4]. Among organ dysfunction, vascular endothelial damage plays an important role by increasing vascular permeability, activating the coagulation cascade and compromising regional perfusion in peripheral organs (e.g. kidneys, liver, gut, etc.)[5]. Different methods have been proposed to assess vascular endothelial damage in patients with sepsis[6]. However, biomarkers may potentially help in determining the presence of vascular endothelial injury and its associated with the development of MOF and mortality.

The cell adhesion molecules (CAMs) are a group of trans-membrane proteins that are responsible of the cell adhesion process. These proteins allow cell to interact with the extracellular matrix (ECM), their own cytoskeleton and other cells[7]. In the vascular endothelium, these proteins are responsible of maintain the homeostasis and interact with circulation cells[7]. The three CAMs that have been used as biomarkers of vascular endothelial injury are Vascular Endothelial Growth Factor (VEGF), Intracellular Adhesion Molecule 1 (ICAM-1), and Vascular Cell Adhesion Molecule-1 (VCAM-1). ICAM-1 and VCAM-1 are cell present in the membranes of leukocytes and vascular endothelium, allowing inflammatory cells to transmigrate into nearby tissues[7]. These adhesion molecules

are expressed in large quantities in patients with sepsis and other uncontrolled inflammatory states[8]. They contribute to endothelial surface damage and vascular leakage[5]. VEGF directly influences endothelial fenestrations, with high levels causing vascular leakage[9]. Previous studies have shown that higher serum levels of ICAM-1 and VCAM-1 are associated with more severe forms of neonatal sepsis [10]. Similarly, ICAM-1 gene deletions in mice have been associated with improved mortality and less histological evidence of organ damage compared to controls with sepsis [5]. Limited data are available regarding the role of ICAM-1 and VCAM-1 in patients with sepsis. In addition, studies evaluating VEGF's role in sepsis have not produced consistent results [11,12]. Therefore, more studies are needed to evaluate the role of these biomarkers in predicting outcomes of sepsis.

ICAM-1, VCAM-1 and VEGF play an important role in vascular endothelial integrity and have a potential clinical application to predict disease progression and clinical outcomes in patients with sepsis. The objective of this study is to determine if elevated levels of endothelial adhesion molecules are associated with (MOF) and increased in-hospital mortality in adult patients with severe sepsis and septic shock. If higher levels are indeed associated with poor outcomes, then rising levels of these markers can be used to predict clinical deterioration and could be used as potential diagnostic tool and therapeutic targets.

## MATERIAL AND METHODS

Study Design

This study is a secondary analysis of a cohort of patients admitted to the intensive care unit (ICU) for severe sepsis or septic shock at two hospitals (South Texas Veterans Health Care System and University Hospital, San Antonio, TX), between 2007 and 2012. The study was approved by the local institutional review board (HSC20070713H), and is posted on www.clinicaltrials.gov (NCT00708799). All participants signed a consent form before entry into the study.

Inclusion criteria for enrollment included age >18 years, informed written consent was obtained from the patient/patient's legal representative, and criteria for severe sepsis or septic shock were met [13]. Exclusion criteria were prolonged QT intervals, medications associated with increased QT intervals, or history of arrhythmias. Patients who were immunosuppressed were also excluded which was defined as: 1) Chemotherapy within the last one month, 2) Leukemia/lymphoma not in remission, 3) Solid organ or bone marrow stem cell transplant, 4) HIV with CD4 <200cells/mm3, and 5) Chronic steroid use defined as > 10mg/day of prednisone.

Enrollment and Follow-Up

All patients were screened for eligibility at the time of admission to the ICU and followed daily until hospital discharge. An Acute Physiology and Chronic Health Evaluation (APACHE II) score was obtained for each patient during the first 24-hours of admission to the ICU [14].

Clinical Outcomes

The primary outcome of this study was development of MOF and the secondary outcome was in-hospital mortality.

Biomarkers and Assays

Venous blood was drawn from patients between 24-48 hours of developing MOF. Serum ICAM-1, VCAM-1 and VEGF were measured using a commercially available Human Inflammation Panel kit from Luminex Technology that was analyzed at Myriad Rules Based Medicine Inc. (Austin Texas.)

Statistical Analysis

Categorical variables were compared between groups using Fisher's exact test. Continuous variables were evaluated using non-parametric analysis using Man-Whitney U Test. Values are expressed as median (IQR). Statistical significance was defined as p-value $\leq$ 0.05. A receiver operating characteristic (ROC) curve was developed to assess the accuracy of ICAM-1, VCAM-1 and VEGF to predict outcomes. Multivariate analysis was performed using multiple logistic regression to evaluate the relation of serum levels of ICAM-1, VCAM-1 and VEGF with the proposed outcomes after adjust the analysis with the APACHE score. All statistical analyses were performed with IBM SPSS, Statistics for Windows, version 22.0. Armonk, NY: IBM Crop.

**RESULTS**

Patient characteristics

Forty-eight patients were included in the study cohort, of which 29 (60%) developed MOF. Tables 1 in patient's demographic characteristics were no statistically differences between the two groups such as age, gender, comorbid-conditions, sources of infection, or previous medication use. Severe septic patients with MOF had higher median (IQR) APACHE II scores on admission (21[15,28] vs. 19[14,21]; p=0.04) compared with those without MOF.

Outcomes

Patients with severe sepsis that developed MOF had higher levels of VCAM-1 (median [IQR] 1,090 ng/mL [789, 1,410] vs. 1,690 ng/mL [1,065, 3,590]; p=0.007) and ICAM-1 (258 ng/mL [199, 341] vs. 362 ng/mL [270, 449]; p=0.01) compared to patients with single organ failure (Figure 1). This association was maintained even after controlling for APACHE II scores in the logistic regression. Figure 2 shows the number of cases of MOF and its relation with the serum levels of VCAM-1, ICAM-1 and VEGF. The area under the curve (AUC) for VCAM-1's association with MOF was 0.71 (Figure 3), and the AUC for ICAM-1 association with MOF was 0.73. There was no statistically significant association between VEGF and the development of MOF (p=0.7).

Only higher VCAM-1 levels showed a statistically significant association with in-hospital mortality (median [IQR] 1,240 ng/mL [806, 1,882] vs. 2,210 ng/mL [1,500, 3,432]; p=0.03). This association was maintained even after controlling for APACHE II scores in the logistic regression. The AUC for VCAM's association with in-hospital

mortality is presented in figure 3. There was no statistically significant association between ICAM-1 and VEGF with hospital mortality.

## DISCUSSION

High levels of VCAM-1 and ICAM-1 were found to be associated with the development of MOF in patients with severe sepsis and septic shock. In this same patient population, only high VCAM-1 level was associated with in-hospital mortality. These associations were maintained even after logistic regression and controlling for overall severity of illness with APACHE II scores. VEGF level was not found to be predictive of MOF or in-hospital mortality.

Previous studies have shown that VCAM-1 is present in low concentrations in the membranes of leukocytes, macrophages, and vascular endothelial cells[5]. Infection increases transcription of VCAM-1 which is expressed on vascular endothelial surfaces[5]. Leukocytes activated by inflammatory mediators bind to the VCAM-1 endothelial surface receptors and translocate into local tissues to combat infection[5]. During states of diffuse and uncontrolled inflammation, as in sepsis, VCAM-1 is expressed in large quantities. The ensuing leukocyte adhesion and associated inflammatory cascade have been linked to vascular endothelial damage, capillary leakage, and organ dysfunction[5]. Several in-vitro studies have demonstrated this phenomenon, but few clinical studies have evaluated the significance of elevated VCAM-1 levels in sepsis. One study in neonates demonstrated higher levels of VCAM-1 associated with more severe forms of sepsis and MOF[15]. These findings are consistent with our study that found elevated serum levels of VCAM-1 at the onset of organ dysfunction predicted development of MOF in adult patients with severe

sepsis and septic shock. However, there is a paucity of data evaluating the association of VCAM-1 levels with the clinical outcome of mortality. Our study was novel in that in-hospital mortality was assessed, and in-hospital mortality was indeed associated with higher VCAM-1 levels.

During inflammatory states, ICAM-1 has the same role as VCAM-1 as a vascular endothelial surface receptor allowing leukocytes and other inflammatory cells to bind and translocate into local tissues[5]. Thus, ICAM-1 plays a similar role in capillary leakage and organ dysfunction when the normal localized inflammatory cascade becomes uncontrolled[5]. Considering these similarities to VCAM-1, previous studies have shown that higher levels of ICAM-1 are associated with severe sepsis and MOF in neonates[10]. Furthermore, multiple mouse models have shown that ICAM-1 knockout mice with severe forms of sepsis have lower mortality rates[5,16]. Our finding that higher levels of ICAM-1 predict development of MOF in patients with severe sepsis and septic shock is a novel finding in the adult population.

In contrast to studies with mouse models, ICAM-1 levels were not associated with increased in-hospital mortality in our sample of adult patients with severe sepsis and septic shock. A lack of statistical association may be due to the small sample size of our study. Another possibility is the role of VCAM-1 may be more pronounced in the inflammatory cascade than ICAM-1 and therefore, VCAM-1 levels were found to correlate with vascular endothelial damage and poor clinical outcomes. However this speculation requires further testing to confirm.

Similar to VCAM-1 and ICAM-1, VEGF also plays an integral role in the integrity of vascular endothelium. VEGF has been shown to induce the expression of both VCAM-

1 and ICAM-1, and contribute to vascular endothelial damage and capillary leakage due to up-regulation during sepsis[17]. Unlike VCAM-1 and ICAM-1, VEGF has a multitude of other roles. In adults with sepsis, high VEGF levels have been shown to increase vascular permeability by binding to the tyrosine-protein kinase receptor-1 (FLT-1), altering the configuration of endothelial actin filaments, and increasing fenestrations in the endothelium[18]. Consequently, the vascular endothelium is made susceptible to damage, ultimately resulting in organ dysfunction[18]. FLT-1 receptor blockers/anti-VEGF receptor antibodies have been shown to decrease mortality in septic mice[18]. VEGF also has a procoagulant effect, causing microthrombi in peripheral vasculature[18]. Considering these plausible associations of elevated VEGF levels with increased sepsis severity vascular damage, human clinical studies have yielded less consistent results on mortality[11,12]. In contrast, in our study VEGF levels were not associated with MOF or mortality, but were consistent with the study done by Karlsson et al. 2008 [12], who had a sample size of 215 patients with severe sepsis and septic shock. Although our sample size may explain the lack of an association between VEGF and clinically important outcomes, Van Der Flier et al. in 2005 showed a positive association of VEGF levels and mortality in a sample size of only 18 septic adult patients[11]. Baseline patient characteristics may explain these findings, but further investigation is required. Of important note, Jiang et al. 2014[19] found that VEGF-to-Platelet ratio was predictive of 28-day mortality in patients with sepsis in China, illustrating the need to further investigation.

Our study has some limitations. That includes the limited of well-characterized group of patients with severe sepsis and septic shock. Generalization of these results

requires further exploration in larger cohorts. Several other mechanisms may be associated to the development of MOF beyond the endothelial adhesion molecules.

## CONCLUSIONS

High levels of VCAM-1 and ICAM-1 at the onset of acute organ dysfunction are associated with the development of MOF, with high VCAM-1 levels also associated with higher in-hospital mortality. These biomarkers have the potential to assist in early recognition and initiation of appropriate therapies to ultimately improve clinical outcomes. Further studies are needed to investigate the role of VCAM-1, ICAM-1, and VEGF as prognostic markers in patients with sepsis. Unlike the non-specific therapeutic targets of corticosteroids and statins, these biomarkers have specific receptors that warrant further investigation as potential therapeutic targets to attenuate the inflammatory cascade during sepsis.

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**Figure legends**

**Figure 1.** Boxplots representing serum levels of VCAM-1 (**Panel A**), ICAM-1 (**Panel B**) and VEGF (**Panel C**) according to multiorgan failure (MOF) and survival status.

**Figure 2.** Distribution of VACM-1, ICAM-1 and VEGF levels by the number of subjects according to the presence or absence of multiorgan failure (MOF).

**Figure 3.** ROC curves of VCAM-1 (**Panel A**), ICAM-1 (**Panel B**) and VEGF (**Panel C**) predict multi organ failure (MOF) and hospital mortality.

**Tables**

**Table 1.** Baseline characteristics of patients with severe sepsis stratified according to the presence of multiorgan failure (MOF)

| Characteristic | No MOF (n=19) | MOF (n=29) | *p* Value |
|---|---|---|---|
| **Demographic** | | | |
| Male | 19 (100) | 27 (93) | 0.6 |
| Age, mean (IQR*) | 59 (51, 65) | 58 (45, 79) | 0.6 |
| **Comorbid conditions, n (%)** | | | |
| Obesity | 7 (37) | 12 (41) | 0.5 |
| Active cancer | 2 (10) | 0 (0) | 0.2 |
| Prior cancer | 3 (16) | 5 (17) | 0.6 |
| Cardiovascular disease | 7 (37) | 5 (17) | 0.1 |
| Chronic heart failure | 3 (16) | 1 (3) | 0.2 |
| COPD | 3 (16) | 3 (10) | 0.4 |
| Chronic kidney disease | 3 (16) | 2 (7) | 0.3 |
| Depression | 2 (10) | 7 (24) | 0.2 |
| Diabetes mellitus | 10 (53) | 13 (45) | 0.4 |
| HIV | 1 (5) | 0 (0) | 0.7 |
| Hyperlipidemia | 4 (17) | 1 (3) | 0.6 |
| Leukemia | 1 (5) | 0 (0) | 0.4 |
| Liver disease | 1 (5) | 2 (7) | 0.6 |
| Tobacco use | 6 (32) | 8 (28) | 0.5 |
| Alcohol use | 4 (21) | 7 (24) | 0.5 |
| Asthma | 1 (5) | 3 (10) | 0.5 |
| **Source of infection, n (%)** | | | |
| Pulmonary | 7 (37) | 8 (28) | 0.5 |
| Urinary tract | 6 (32) | 10 (34) | 0.3 |
| GI | 2 (10) | 4 (14) | 0.4 |
| Skin | 3 (16) | 5 (17) | 0.3 |
| Endocarditis | 0 (0) | 1 (3) | 0.9 |

*** IQR, interquartile range**

**Figure 1.**

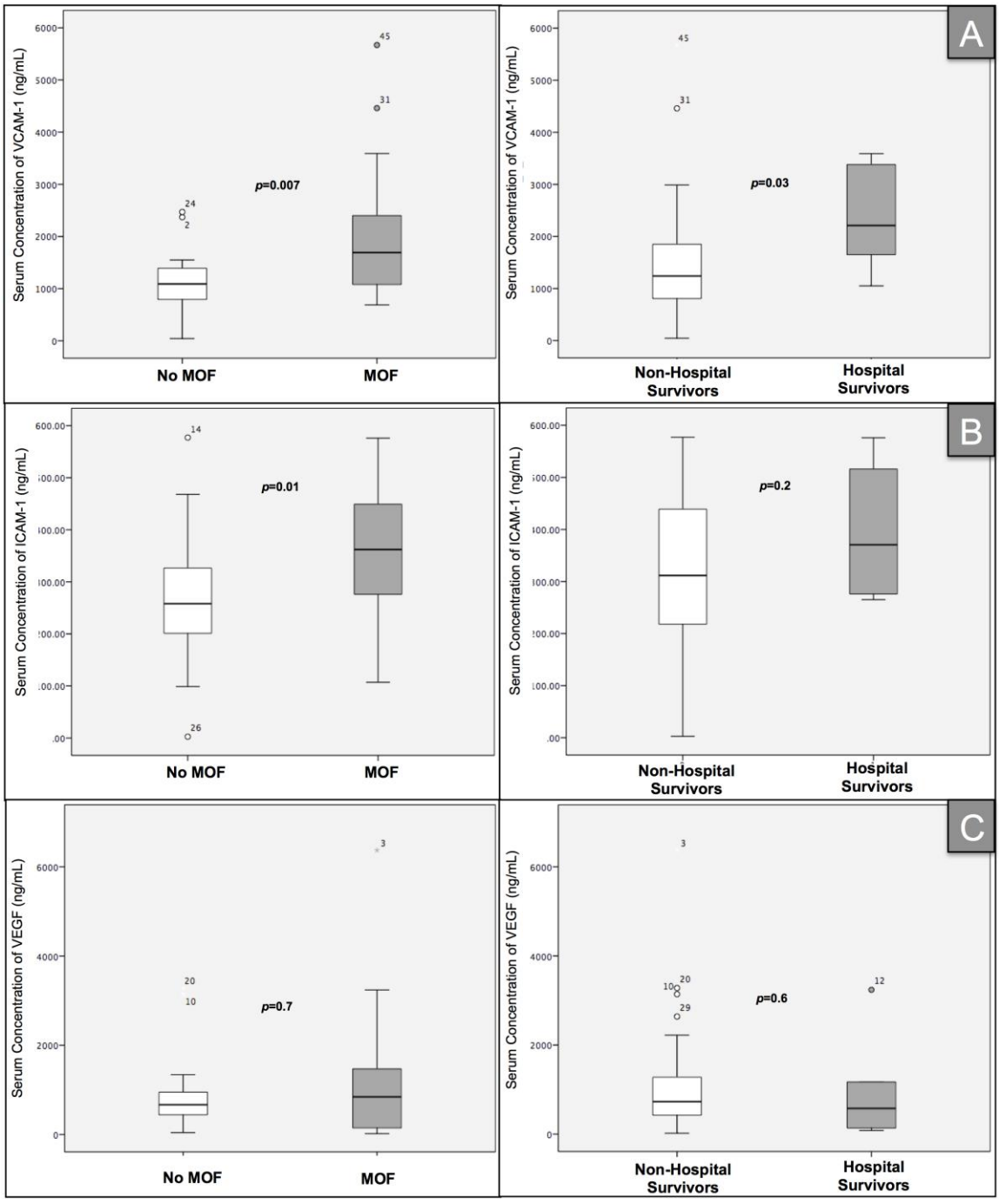

A
Serum Concentration of VCAM-1 (ng/mL)
p=0.007
No MOF
MOF
p=0.03
Non-Hospital Survivors
Hospital Survivors
B
Serum Concentration of ICAM-1 (ng/mL)
p=0.01
No MOF
MOF
p=0.2
Non-Hospital Survivors
Hospital Survivors
C
Serum Concentration of VEGF (ng/mL)
p=0.7
No MOF
MOF
p=0.6
Non-Hospital Survivors
Hospital Survivors

**Figure 2.**

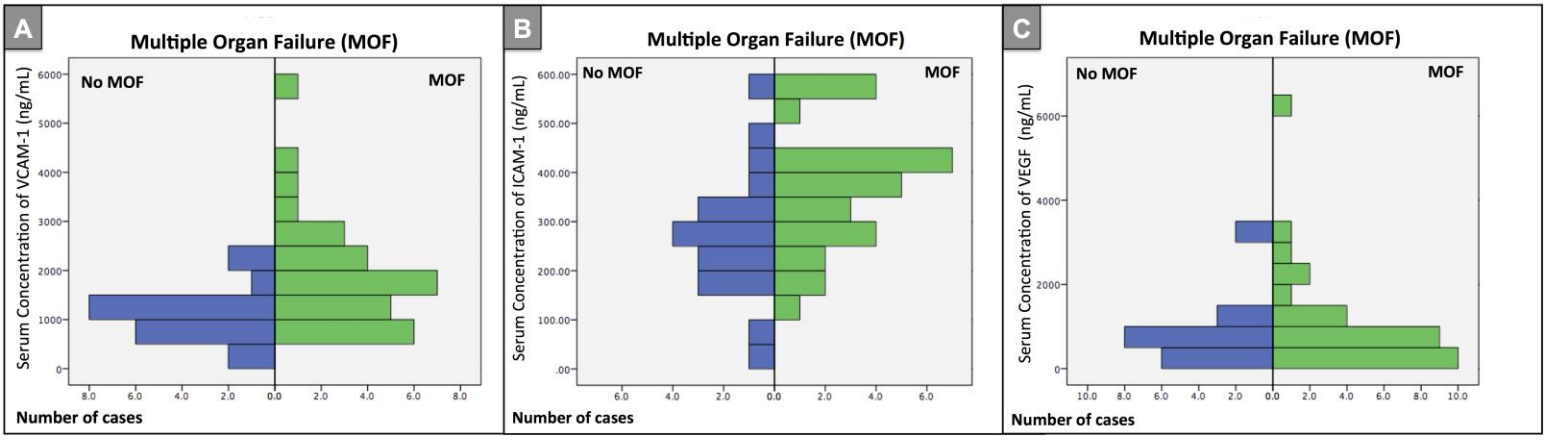
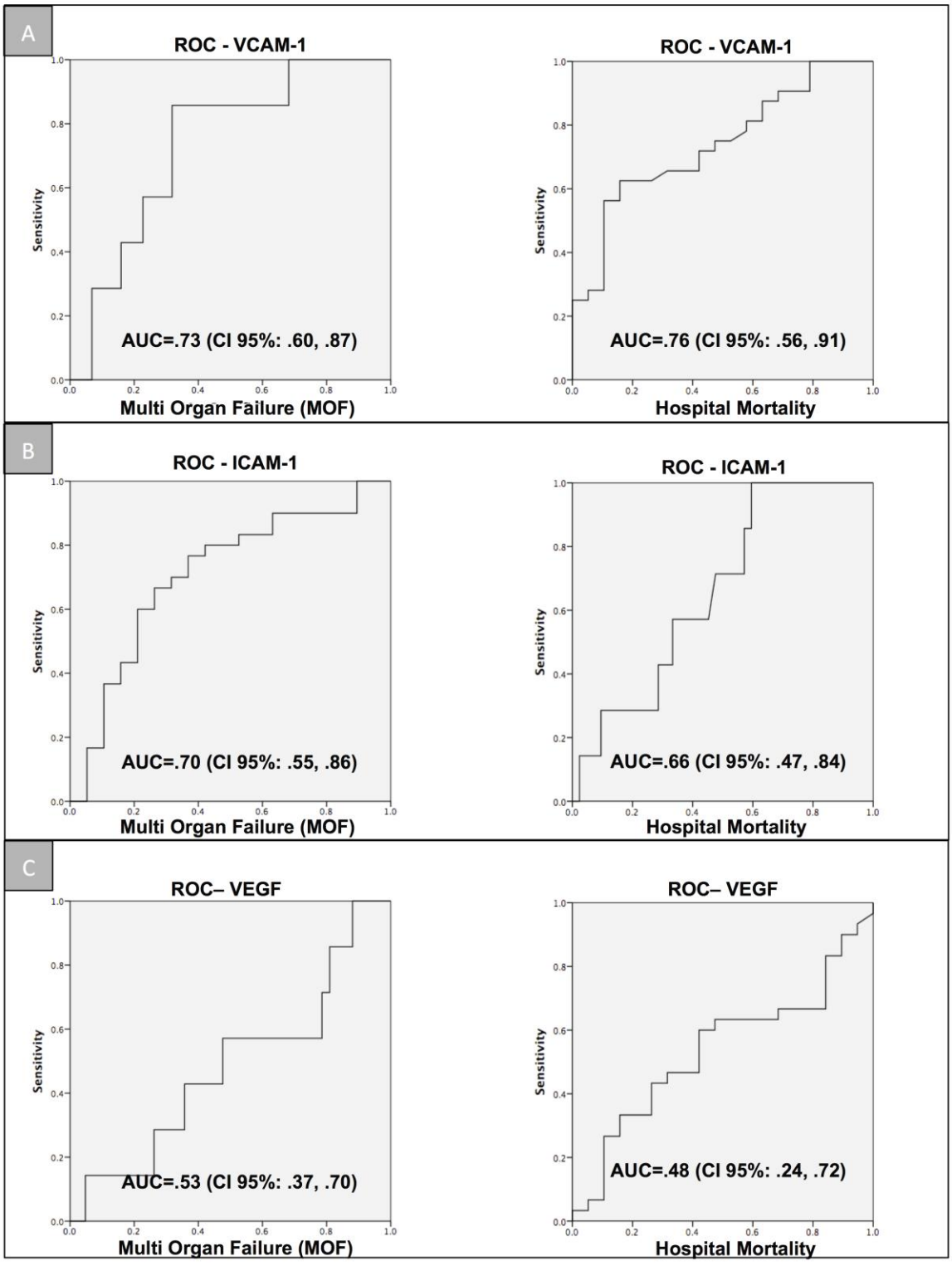



**Figure 3.**


A
ROC - VCAM-1
Sensitivity
AUC=.73 (CI 95%: .60, .87)
Multi Organ Failure (MOF)
ROC - VCAM-1
Sensitivity
AUC=.76 (CI 95%: .56, .91)
Hospital Mortality
B
ROC - ICAM-1
Sensitivity
AUC=.70 (CI 95%: .55, .86)
Multi Organ Failure (MOF)
ROC - ICAM-1
Sensitivity
AUC=.66 (CI 95%: .47, .84)
Hospital Mortality
C
ROC– VEGF
Sensitivity
AUC=.53 (CI 95%: .37, .70)
Multi Organ Failure (MOF)
ROC– VEGF
Sensitivity
AUC=.48 (CI 95%: .24, .72)
Hospital Mortality